AD_____

Award Number: W81XWH-06-1-0452

TITLE: Crosstalk between Leptin Receptor and IGF-IR in Breast Cancer: A Potential Mediator of Chemoresistance

PRINCIPAL INVESTIGATOR: Rita Nahta, Ph.D.

CONTRACTING ORGANIZATION: The University of Texas
M.D. Anderson Cancer Center
Houston, TX 77030

REPORT DATE: April 2007

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-04-2007	Annual	20 Mar 2006 – 19 Mar 2007

4. TITLE AND SUBTITLE

Crosstalk between Leptin Receptor and IGF-IR in Breast Cancer: A Potential Mediator of Chemoresistance

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-06-1-0452

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Rita Nahta, Ph.D.

Email: rnahta@emory.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The University of Texas
M.D. Anderson Cancer Center
Houston, TX 77030

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
Original contains colored plates: ALL DTIC reproductions will be in black and white.

14. ABSTRACT

Obesity is a major risk factor for the development and progression of breast cancer, and is associated with reduced treatment response and reduced overall survival. The obesity-associated hormones IGF-I and leptin are found at high levels in the serum of breast cancer patients, and their receptors, IGF-IR and the leptin receptor (Ob-R) are overexpressed in a majority of breast tumor tissues. We have discovered by co-immunoprecipitation that IGF-IR and Ob-R physically interact in breast cancer cells. This interaction was associated with cross talk from IGF-IR to Ob-R, as IGF-I stimulation promoted signaling downstream of the leptin receptor, including increased phosphorylation of Ob-R, STAT3, and JAK2. Our preliminary data suggests that this cross talk is unidirectional, as leptin stimulation did not alter IGF-IR phosphorylation. Our ongoing studies will examine this cross talk in more detail, in part by determining the biological and molecular effects of inhibition of these growth factor receptors. We will then examine the influence of this cross talk on response to taxane-based chemotherapy.

15. SUBJECT TERMS
Breast cancer, leptin, insulin-like growth factor-I, growth factor receptor signaling

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	17	USAMRMC

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

INTRODUCTION

Obesity is an important risk factor associated with the development and progression of breast cancer (1-7), reduced therapeutic efficacy, and higher mortality rates among breast cancer patients (8-11). The obesity-associated hormones insulin-like growth factor-I (IGF-I) and leptin are found at high levels in breast cancer patients (12-15), and their receptors, IGF-IR and Ob-R (leptin receptor is also known as obesity receptor), are overexpressed in a majority of breast cancers (15-17). Increased expression of leptin and Ob-R correlate with increased risk for distant metastasis and reduced overall survival in breast cancer patients (15). Leptin induces proliferation of breast cancer cells via activation of STAT3 (18,19), a transcriptional activator of the anti-apoptotic protein Bcl-2 (20,21). STAT3-dependent overexpression of Bcl-2 was associated with resistance to the chemotherapeutic agent paclitaxel in breast cancer cells (21). We propose that IGF-IR and the leptin receptor interact, and that IGF-IR and leptin induce phosphorylation of Ob-R, activating STAT3 and upregulating Bcl-2, which in turn results in taxane resistance (illustrated as Figure 1). Our hypothesis is that high levels of leptin and IGF-I increase Ob-R signaling, contributing to taxane resistance in breast cancer. Our long-term goal is to establish markers of Ob-R signaling as predictors of taxane response. The rationale is that these markers of Ob-R signaling, including serum levels of leptin and IGF-I, and tissue levels of phosphorylated Ob-R, STAT3 and Bcl-2, can be used (1) to identify patients most likely to respond to taxanes, and (2) as therapeutic targets to improve response rates to taxanes in the treatment of breast cancer.

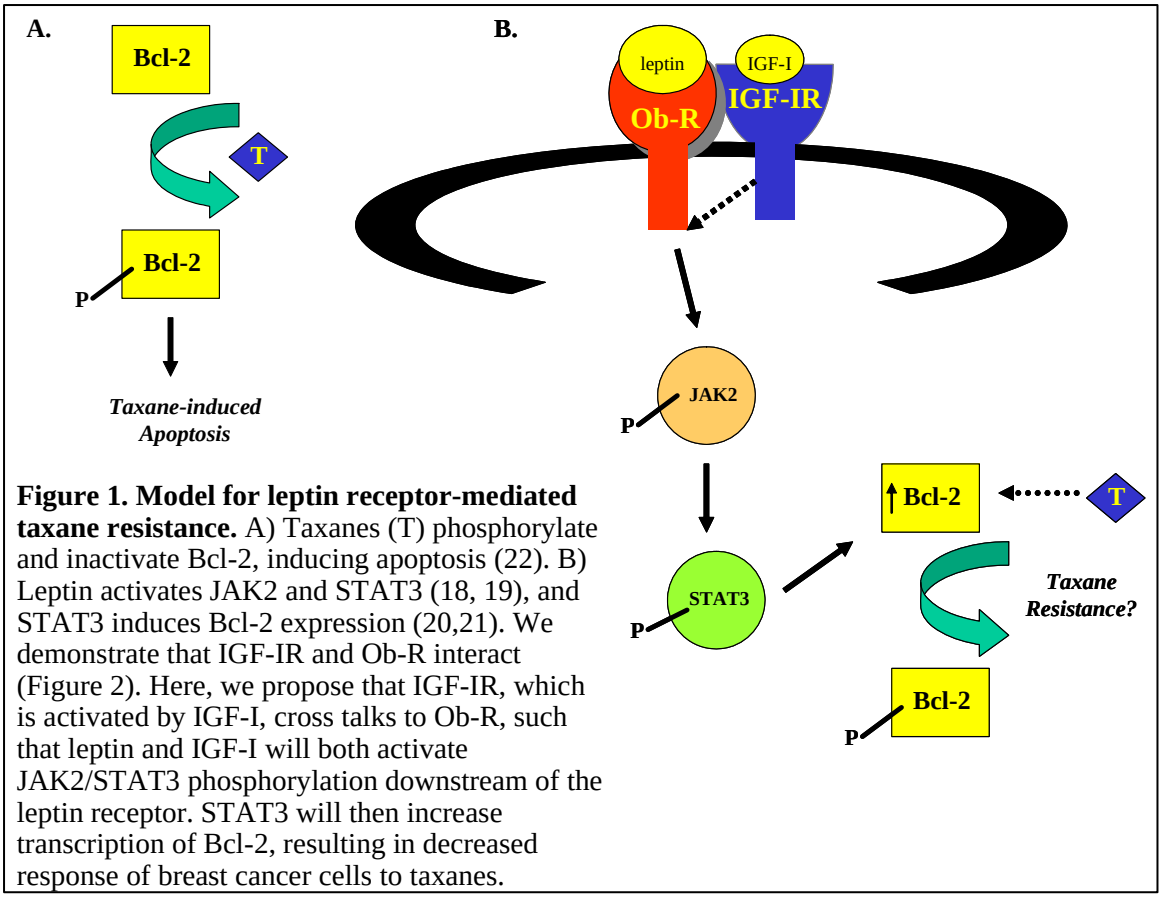

Figure 1. Model for leptin receptor-mediated taxane resistance. A) Taxanes (T) phosphorylate and inactivate Bcl-2, inducing apoptosis (22). B) Leptin activates JAK2 and STAT3 (18, 19), and STAT3 induces Bcl-2 expression (20,21). We demonstrate that IGF-IR and Ob-R interact (Figure 2). Here, we propose that IGF-IR, which is activated by IGF-I, cross talks to Ob-R, such that leptin and IGF-I will both activate JAK2/STAT3 phosphorylation downstream of the leptin receptor. STAT3 will then increase transcription of Bcl-2, resulting in decreased response of breast cancer cells to taxanes.

BODY

Task 1 Apply nanotechnology-based methods for visualization of IGF-IR and leptin receptor (Ob-R) in real time.

This aim is being done in collaboration with Dr. Konstantin Sokolov at MD Anderson. As labeling of antibodies with nanoparticles is often the limiting factor, his team has been working on this technique and has now successfully labeled antibodies with gold or silver nanoparticles. We are working to select the best cell lines to employ for these experiments and the results of the next task will dictate which cell lines we choose. Hence, task1 will continue into year 2. However, a large part of task 2 and part of task 3 has been completed, so there will not be any delay in producing results associated with the aims of the proposed research.

Task 2 Demonstrate that IGF-I activates the leptin receptor via IGF-IR crosstalk.

The breast cancer cell lines MDA-MB-231 (MDA231), MCF7, BT474, and SKBR3 were examined for IGF-IR and leptin receptor expression and interaction. Cells were lysed for protein and leptin receptor was immunoprecipitated from cells. Immunoblotting demonstrated that IGF-IR was pulled down with the leptin receptor, indicating that they form a complex (Figure 2A). Conversely, immunoprecipitation of IGF-IR showed pull down of leptin receptor in all cell lines (Figure 2B). Our preliminary results described in the initial proposal stated that only the MCF7 cell line failed to show interaction between these receptors. However, upon repeating the experiment multiple times, we have consistently observed that the interaction occurs in all four of the lines tested, including MCF7 cells.

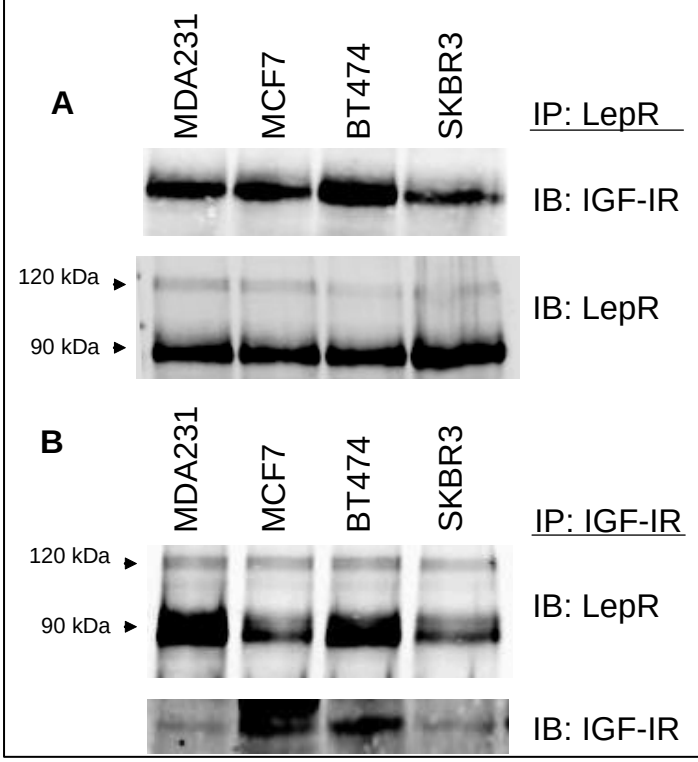

Figure 2. IGF-IR and leptin receptor interact in breast cancer cells. (A) Leptin receptor (LepR) was immunoprecipitated (IP) from breast cancer cell lysates and immunoblotted for IGF-IR and leptin receptor. Pull down of leptin receptor was similar among all samples, indicating similar expression level among cell lines. Both isoforms of leptin receptor are shown. IGF-IR was also pulled down in the leptin receptor IPs, indicating that the receptors form a protein complex. (B) The reverse IP was performed and immunoblotted for leptin receptor and IGF-IR. IGF-IR expression varies among cell lines. Leptin receptor is in a complex with IGF-IR in all lines.

Total receptor levels were also examined in the cell lines (Figure 3). The leptin receptor has two isoforms. The long isoform is approximately 120 kDa, and possesses kinase activity. The short isoform is 90 kDa and lacks signaling capability, and its function is unclear. All cells showed expression of the long isoform of the leptin receptor, with BT474 cells showing very low levels of the short isoform. IGF-IR expression varied among lines, with MCF7 and BT474 cells showing highest levels.

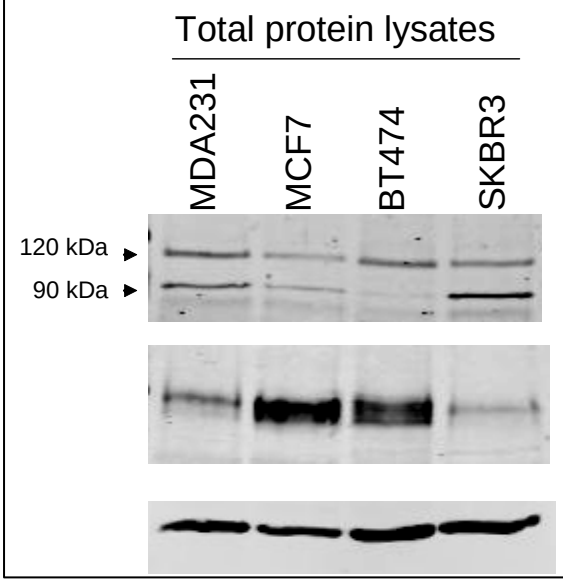

Figure 3. IGF-IR and leptin receptor expression in breast cancer cells. Total protein lysates were immunoblotted for leptin receptor and IGF-IR. The H-300 leptin receptor antibody (Santa Cruz Biotechnology) recognizes both isoforms. All four cell lines express the long isoform, which is the isoform with kinase activity; BT474 cells show low levels of the short isoform. IGF-IR is expressed at high levels in MCF7 and BT474 cells, and lower levels in MDA231 and SKBR3 cells.

We next wanted to determine the functional consequence of this interaction. MCF7 cells were serum starved overnight to remove hormonal stimulation. Cells were then stimulated with 100ng/mL IGF-I for the indicated time course (Figure 4A). Cells were lysed for protein, and immunoblots were performed for total and phosphorylated leptin receptor (using phospho-tyrosine 1141- specific antibody for leptin receptor, Santa Cruz Biotechnology), and for total and phosphorylated IGF-IR (using anti-phospho-tyrosine 1162/1163 insulin receptor/IGF-IR antibody, Biosource). IGF-IR phosphorylation was stimulated within 5 minutes (min). Importantly, leptin receptor phosphorylation was also stimulated within 5 min, indicating that IGF-IR activation corresponds with activation of leptin receptor, suggesting potential cross talk from IGF-IR to leptin receptor. Total levels of IGF-IR and leptin receptor isoforms did not change. Downstream of the receptors, the signaling pathways including JAK2, STAT3, ERK1/2, and Akt were examined (Figure 4B). The major molecules activated were JAK2 and ERK1/2, and to a lesser extent STAT3 and Akt. We have also confirmed these results in another cell line, MDA231, in which we also observed phosphorylation of leptin receptor in response to IGF-I stimulation (Figure 5A) and activation of JAK2 and ERK1/2 as the major changes in downstream signaling (Figure 5B). Hence, the potential biological consequences of IGF-IR cross talk to leptin receptor may be mediated by the JAK2 and MAPK signaling pathways, and remain to be examined. Thus, we will follow up these results in year 2 by inhibiting IGF-IR, JAK2, and ERK1/2, as described in the original proposal, and examining the molecular effects on cross talk and the biological effects on these cancer lines.

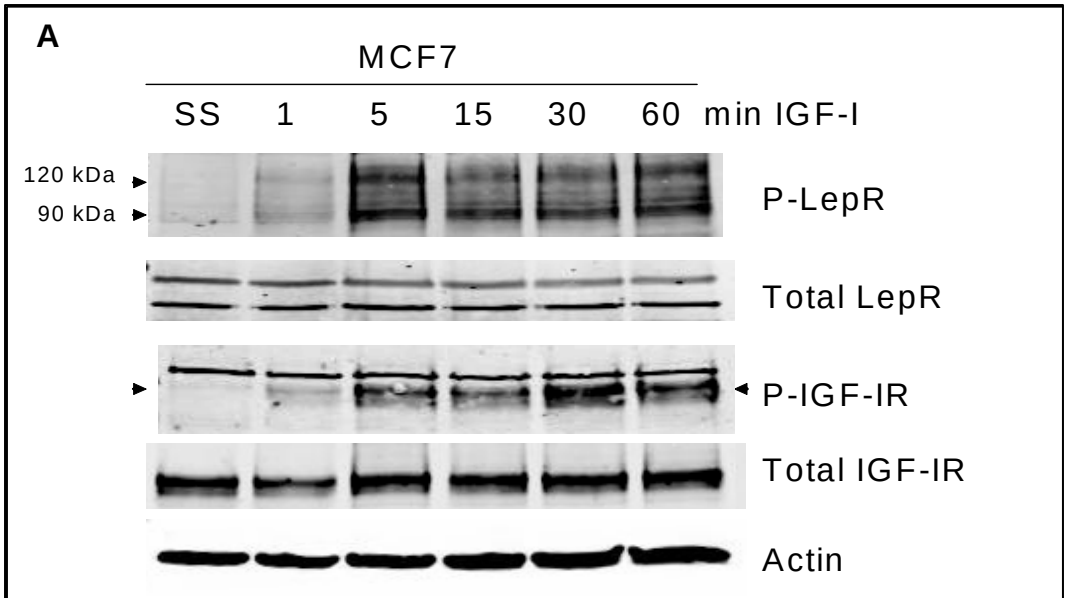

Figure 4A. IGF-I stimulates phosphorylation of leptin receptor in MCF7 breast cancer cells: evidence of receptor cross talk. MCF7 cells were serum starved overnight, and then stimulated with IGF-I (100 ng/mL) for 1, 5, 15, 30, or 60 minutes (min). SS indicates the serum starved, non-stimulated control. Within 5 minutes of stimulation, IGF-IR was phosphorylated as expected. Total IGF-IR levels were unchanged. Interestingly, leptin receptor (LepR) was also phosphorylated within 5 minutes, indicating that activation of IGF-IR corresponds with activation of LepR, suggesting cross talk from IGF-IR to leptin receptor. Total levels of both isoforms of LepR were unchanged.

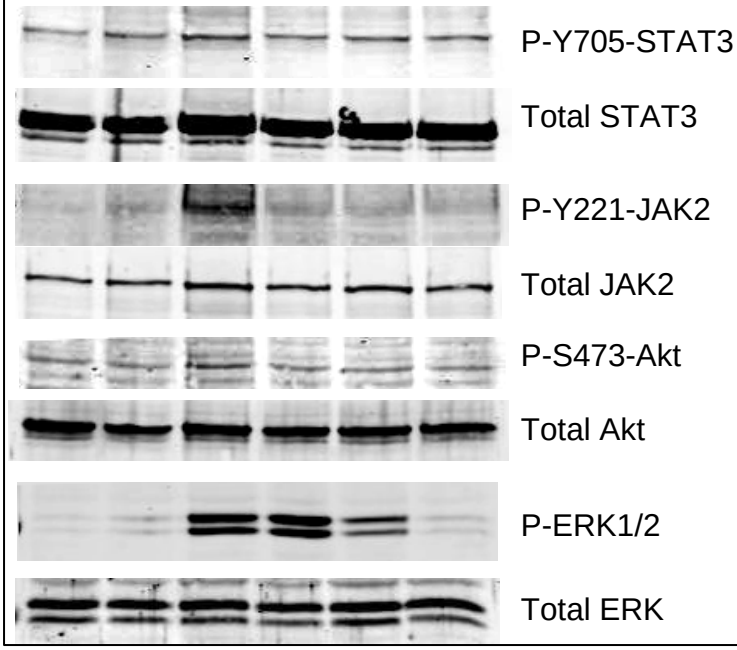

Figure 4B. IGF-I activates leptin receptor signaling in MCF7 breast cancer cells: evidence of receptor cross talk. MCF7 cells were serum starved overnight, and then stimulated with IGF-I (100 ng/mL) for 1, 5, 15, 30, or 60 minutes (min). SS indicates the serum starved, non-stimulated control. JAK2 and, to a lesser extent, STAT3 were phosphorylated within 5 min of IGF-I stimulation, as were ERK1 and ERK2 and, to a lesser extent, Akt. Thus, the main downstream molecules activated were JAK2 and ERK1/2.

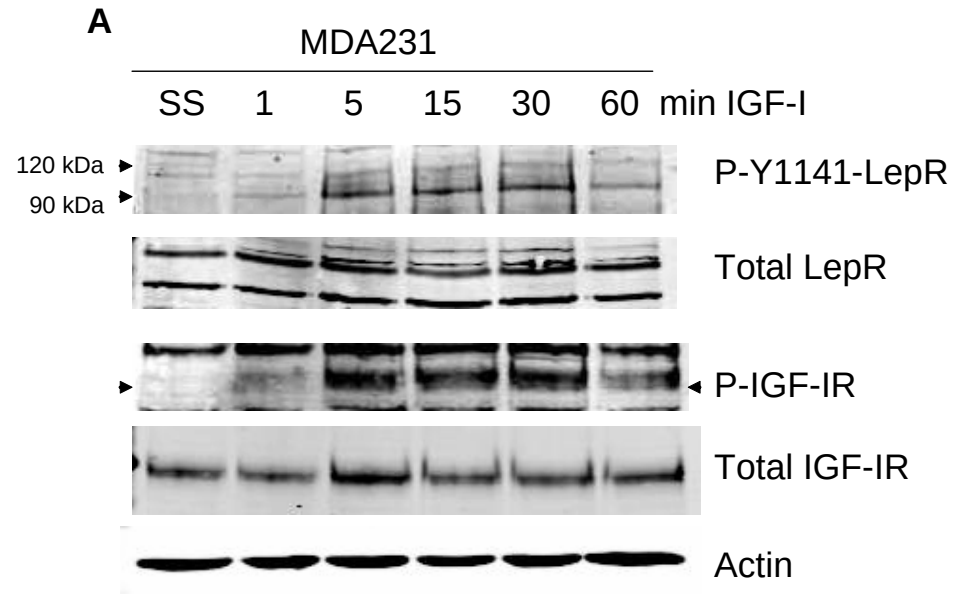

Figure 5A. IGF-I stimulates phosphorylation of leptin receptor in MDA231 breast cancer cells: evidence of receptor cross talk. MDA231 cells were serum starved overnight, and then stimulated with IGF-I (100 ng/mL) for 1, 5, 15, 30, or 60 minutes (min). SS indicates the serum starved, non-stimulated control. Within 5 minutes of stimulation, IGF-IR was phosphorylated as expected. Total IGF-IR levels were unchanged. Interestingly, leptin receptor (LepR) was also phosphorylated within 5 minutes, indicating that activation of IGF-IR corresponds with activation of LepR, suggesting cross talk from IGF-IR to leptin receptor. Total levels of both isoforms of LepR were unchanged. These results are similar to what was observed in MCF7 cells.

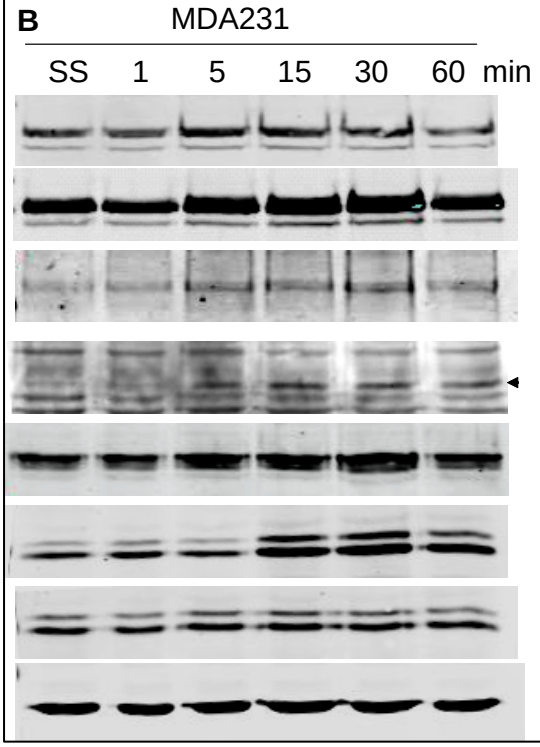

Figure 5B. IGF-I activates leptin receptor signaling in MDA231 breast cancer cells: evidence of receptor cross talk. MDA231 cells were serum starved overnight, and then stimulated with IGF-I (100 ng/mL) for 1, 5, 15, 30, or 60 minutes (min). SS indicates the serum starved, non-stimulated control. JAK2 and, to a lesser extent, STAT3 were phosphorylated within 5 min of IGF-I stimulation, as were ERK1 and ERK2 and, to a lesser extent, Akt. Thus, the main downstream molecules activated were JAK2 and ERK1/2, similar to results seen in MCF7 cells.

Cross talk in the opposite direction, from leptin receptor to IGF-IR, was also examined. For this experiment, MCF7 cells were serum starved overnight, and stimulated with 100ng/mL leptin for the indicated time points (Figure 6). Immunoblots of total lysates were probed for phospho-leptin receptor and phospho-IGF-IR. Our preliminary results indicated that leptin receptor is phosphorylated as expected, although the quality of the blot is weak and must be repeated. However, a signal was not detected for phospho-IGF-IR. Thus, a positive control for IGF-I-stimulated cells must be included on the next blot to confirm if this indicates that leptin does not promote phosphorylation of IGF-IR, suggesting that the cross talk is unidirectional. Hence, in year 2, this aim will be continued by examining leptin receptor cross talk to IGF-IR. We will also examine the effects of this cross talk on Bcl-2 as described in the original proposal.

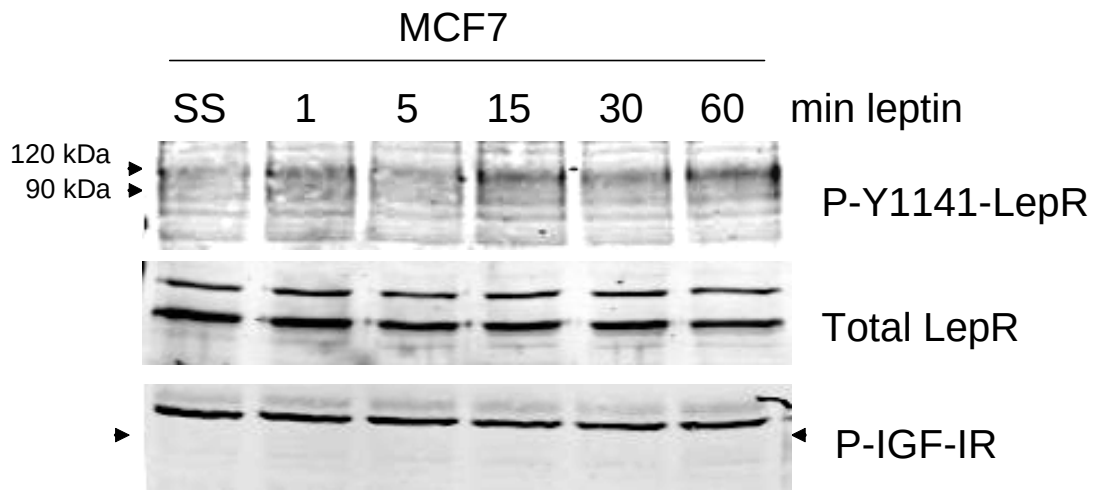

Figure 6. Leptin does not induce phosphorylation of IGF-IR: evidence of potential unidirectional receptor cross talk. MCF7 cells were serum starved overnight, and then stimulated with leptin (100 ng/mL) for 1, 5, 15, 30, or 60 minutes (min). SS indicates the serum starved, non-stimulated control. No change in IGF-IR phosphorylation status was observed. As discussed in the text, the quality of this preliminary blot is weak and must be repeated several times. In addition, a positive control is required for p-IGF-IR to ensure that leptin is actually not inducing phosphorylation of IGF-IR.

Task 3 Demonstrate that Ob-R signaling activated by leptin or IGF-I contributes to taxane resistance.

MCF7, BT474, and SKBR3 cells were either untreated, treated with 100ng/mL leptin for 36 hours (h), 5nM docetaxel for 24 h, or treated with a combination of leptin and docetaxel, where cells were pre-treated with leptin for 12 hours and then docetaxel was added to the media for an additional 24 hours. DNA fragmentation as a measure of apoptosis was examined using the Cell Death ELISA Plus Kit (Roche Applied Science) per manufacturer instructions. With this particular experimental design, very little change in DNA fragmentation was observed in MCF7 and BT474 cells (Figure 7). In SKBR3

cells docetaxel alone caused a 2-fold increase in DNA fragmentation, and the added contribution of leptin was negligible. Hence, these negative results will be followed up by testing other doses and time points, as well as other assays (flow cytometry, trypan blue exclusion), as described in the original proposal. We are also working in collaboration with other investigators at MD Anderson to examine association of leptin receptor signaling molecules with resistance to taxanes in breast cancer patients, as described for years 2 and 3 of the proposal.

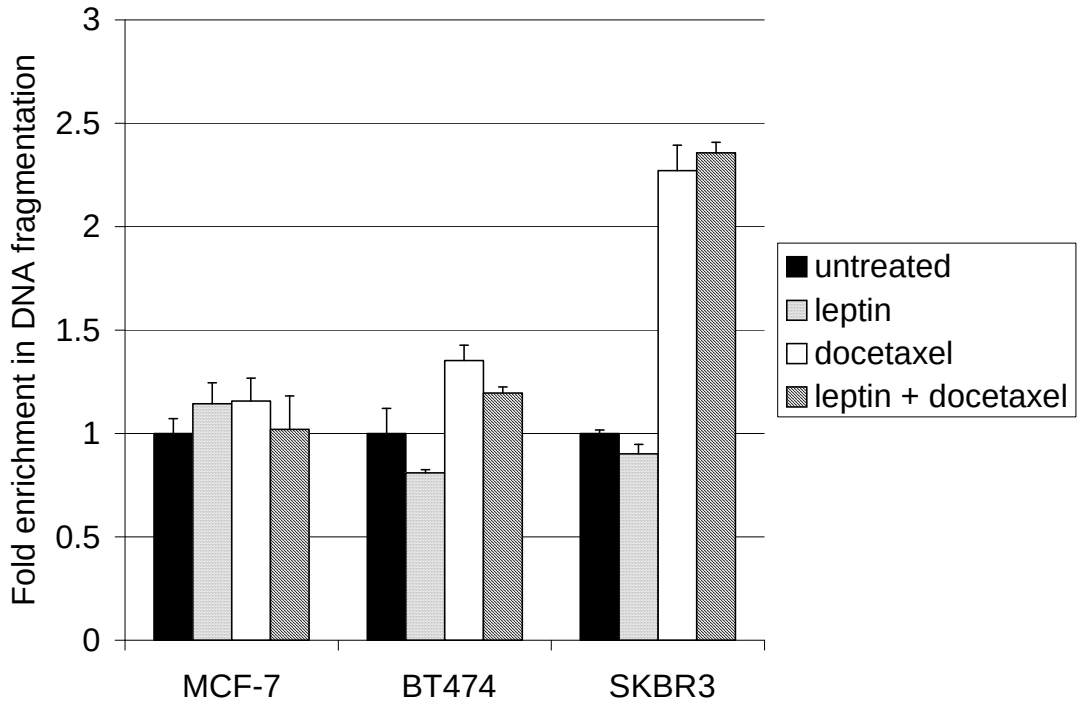

Figure 7. Effect of leptin on taxane-stimulated DNA fragmentation. MCF7, BT474, and SKBR3 cells were stimulated with leptin (100 ng/mL) for 12 h (overnight). Docetaxel (5nM) was then added for 24 h. Cell lysates were examined for DNA fragmentation as a measure of apoptosis (Cell Death ELISA Plus, Roche). Fold enrichment in DNA fragmentation using untreated cells as a control is shown for each cell line. Leptin did not inhibit apoptosis. However, docetaxel did not induce significant apoptosis except for a 2-fold increase in SKBR3 cells. Hence, the experimental design may need to be improved to accurately test our hypothesis. We will examine different doses and time points and use the other assays for measuring apoptosis described in the original proposal.

KEY RESEARCH ACCOMPLISHMENTS

- ❖ Discovery that IGF-IR and leptin receptor interact
- ❖ Discovery that IGF-I promotes leptin receptor phosphorylation

REPORTABLE OUTCOMES

- ❖ The grant recipient was selected to become a tenure track faculty member, in part based on the project funded through this award. (Please see the attached CV of the recipient in the attached appendix.)

CONCLUSION

We demonstrate that IGF-IR and Ob-R physically interact in breast cancer cells. We also show evidence that IGF-I stimulates phosphorylation of leptin receptor. We will confirm cross talk from IGF-IR by inhibiting IGF-IR in the presence of IGF-I and blotting for phosphorylated leptin receptor. Our preliminary data suggests that the cross talk may be unidirectional; however, we must perform the leptin stimulation experiments using the proper control (IGF-I-stimulated cells) and improve the quality of the immunoblots to determine if in fact leptin does not stimulate IGF-IR phosphorylation. Our future experiments will also examine the effect of this cross signaling on Bcl2, and on taxane responsiveness. The results so far are significant in that they suggest interaction between two growth factor receptor signaling pathways that play an important part in breast cancer biology. In fact, multiple agents targeted against IGF-IR are being developed for clinical use. The implication is that targeting one receptor may not be enough; dual targeting against IGF-IR and leptin receptor may be more appropriate if our hypotheses are proven. In addition, determining the role of these receptor pathways in taxane responsiveness will be important towards improving prediction of who will respond to this commonly used chemotherapeutic agent.

REFERENCES

1. Morimoto LM, White E, Chen Z, Chlebowski RT, Hays J, Kuller L, Lopez AM, Manson J, Margolis KL, Muti PC, Stefanick ML, McTiernan A. (2002) Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes Control 13: 741-751.

2. Sweeney C, Blair CK, Anderson KE, Lazovich D, Folsom AR. (2004) Risk factors for breast cancer in elderly women. Am J Epidemiol 160: 868-875.

3. Maehle BO, Tretli S, Thorsen T. (2004) The associations of obesity, lymph node status and prognosis in breast cancer patients: dependence on estrogen and progesterone receptor status. APMIS 112: 349-357.

4. Chlebowski RT. (2005) Obesity and early-stage breast cancer. J Clin Oncol 23: 1345-1347.

5. Camoriano JK, Loprinzi CL, Ingle JN, Therneau TM, Krook JE, Veeder MH. (1990) Weight change in women treated with adjuvant therapy or observed following mastectomy for node-positive breast cancer. J Clin Oncol 8: 1327-1334.

6. Irwin ML, McTiernan A, Baumgartner RN, Baumgartner KB, Bernstein L, Gilliland FD, Ballard-Barbash R. (2005) Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. J Clin Oncol 23: 774-782.

7. Kroenke CH, Chen WY, Rosner B, Holmes MD. (2005) Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 23: 1370-1378.

8. Tormey DC, Gray R, Gilchrist K, Grage T, Carbone PP, Wolter J, Woll JE, Cummings FJ. (1990) Adjuvant chemohormonal therapy with cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone (CMFP) or CMFP plus tamoxifen compared with CMF for premenopausal breast cancer patients. An Eastern Cooperative Oncology Group trial. Cancer 65: 200-206.

9. Bastarrachea J, Hortobagyi GN, Smith TL, Kau SW, Buzdar AU. (1994) Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. Ann Intern Med 120: 18-25.

10. Berclaz G, Li S, Price KN, Coates AS, Castiglione-Gertsch M, Rudenstam CM, Holmberg SB, Lindtner J, Erien D, Collins J, Snyder R, Thurlimann B, Fey MF, Mendiola C, Werner ID, Simoncini E, Crivellari D, Gelber RD, Goldhirsch A; International Breast Cancer Study Group. (2004) Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. Ann Oncol 15: 875-884.

11. Enger SM, Greif JM, Polikoff J, Press M. (2004) Body weight correlates with mortality in early-stage breast cancer. Arch Surg 139: 954-958; discussion 958-960.

12. Schernhammer ES, Holly JM, Pollak MN, Hankinson SE. (2005) Circulating levels of insulin-like growth factors, their binding proteins, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 14: 699-704.

13. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M. (1998) Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 351: 1393-1396.

14. Tessitore L, Vizio B, Jenkins O, De Stefano I, Ritossa C, Argiles JM, Benedetto C, Mussa A. (2000) Leptin expression in colorectal and breast cancer patients. Int J Mol Med 5: 421-426.

15. Ishikawa M, Kitayama J, Nagawa H. (2004) Enhanced expression of leptin and leptin receptor (OB-R) in human breast cancer. Clin Cancer Res 10: 4325-4331.

16. Cullen KJ, Yee D, Sly WS, Perdue J, Hampton B, Lippman ME, Rosen N. (1990) Insulin-like growth factor receptor expression and function in human breast cancer. Cancer Res 50: 48-53.

17. Resnik JL, Reichart DB, Huey K, Webster NJ, Seely BL. (1998) Elevated insulin-like growth factor I receptor autophosphorylation and kinase activity in human breast cancer. Cancer Res 58:1159-1164.

18. Banks AS, Davis SM, Bates SH, Myers MG Jr. (2000) Activation of downstream signals by the long form of the leptin receptor. J Biol Chem 275:14563-14572.

19. Yin N, Wang D, Zhang H, Yi X, Sun X, Shi B, Wu H, Wu G, Wang X, Shang Y. (2004) Molecular mechanisms involved in the growth stimulation of breast cancer cells by leptin. Cancer Res 64: 5870-5875.

20. Stephanou A, Brar BK, Knight RA, Latchman DS. (2000) Opposing actions of STAT-1 and STAT-3 on the Bcl-2 and Bcl-x promoters. Cell Death Differ 7: 329-330.

21. Real PJ, Sierra A, De Juan A, Segovia JC, Lopez-Vega JM, Fernandez-Luna JL. (2002) Resistance to chemotherapy via Stat3-dependent overexpression of Bcl-2 in metastatic breast cancer cells. Oncogene 21: 7611-7618.

22. Haldar S, Jena N, Croce CM. (1995) Inactivation of Bcl-2 by phosphorylation. Proc Natl Acad Sci U S A 92: 4507-4511.

APPENDICES

Please see the attached Curriculum Vitae.

SUPPORTING DATA

N/A

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Rita Nahta	Assistant Professor
eRA COMMONS USER NAME rnahta	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of North Carolina, Chapel Hill, NC	B.S.	1994	Chemistry
Duke University, Durham, NC	Ph.D.	2000	Pathology and Molecular Medicine
Harvard Medical School, Boston, MA	N/A	2000-2002	Postdoctoral
M. D. Anderson Cancer Center, Houston, TX	N/A	2002-2004	Postdoctoral

Please refer to the application instructions in order to complete sections A, B, and C of the Biographical Sketch.

A. Positions and Honors.

Positions and Employment

1990-1994 Lab Technician, Analytical and Environmental Chemistry Laboratory, The Virkler Company, Charlotte, N.C. (summers)

1995-2000 Ph.D. Candidate, Department of Pathology and Molecular Medicine, Duke University, Durham, N.C., Mentors: J. Dirk Iglehart, M.D., Professor, and Jeffrey R. Marks, Ph.D., Associate Professor

2000-2002 Postdoctoral Fellow, Department of Medicine and Tumor Biology, Harvard Medical School and Massachusetts General Hospital Cancer Center, Boston, MA, Mentor: Emmett V. Schmidt, M.D., Ph.D., Associate Professor

2002-2004 Postdoctoral Fellow, Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, Mentor: Francisco J. Esteva, M.D., Ph.D., Associate Professor

2004-2/2007 Instructor, Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, Mentor: Francisco J. Esteva, M.D., Ph.D., Associate Professor

2/2007-present Assistant Professor, Departments of Pharmacology and Hematology/Oncology, Emory University School of Medicine and Winship Cancer Institute

Other Experience and Professional Memberships

1993-1994 Volunteer Research Assistant, Department of Biology, University of North Carolina, Chapel Hill, N.C.

1994-1995 Volunteer Research Assistant, Department of Biology, University of North Carolina at Charlotte, Charlotte, N.C.

1997-1999 Tutor, General Biology, Chemistry, and English, Duke University Medical Center, Durham, N.C.

1997-2000 Supervisor in the laboratory, Undergraduate Research Program, Duke University Medical Center, Durham, N.C.

2003-7/2006 Associate Member, American Association for Cancer Research (AACR)

8/2006-present Active Member, American Association for Cancer Research (AACR)

2005-present Professional Member, American Association for the Advancement of Science (AAAS)

Honors

1990	North Carolina School of Science & Mathematics Graduate
2001	Invited Attendee, Gordon Research Conference on Chemotherapy and Experimental Therapeutics of Cancer, Colby-Sawyer College, New London, New Hampshire
2004	AACR-Amgen, Inc. Fellowship Award in Clinical/Translational Cancer Research
2004	M. D. Anderson Cancer Center Odyssey Special Fellowship Award
2004	Department of Defense Breast Cancer Research Program Concept Award
2006	Department of Defense Breast Cancer Research Program IDEA Award
2006	National Cancer Institute K01 Career Development Award

B. Peer-reviewed Publications (in chronological order).

Original research articles

1. Dong Q, Johnson SP, Colvin OM, Bullock N, Kilborn C, Runyon G, Sullivan DM, Easton J, Bigner DD, Nahta R, Marks JR, Modrich P, and Friedman HS. Multiple DNA repair mechanisms and alkylator resistance in the human medulloblastoma cell line D-283 Med (4-HCR). Cancer Chemother Pharmacol 43:73-79, 1999.

2. Nahta R, Iglehart JD, Kempkes B, and Schmidt EV. Rate-limiting effects of Cyclin D1 in transformation by ErbB2 predicts synergy between herceptin and flavopiridol. Cancer Res 62: 2267-2271, 2002.

3. Nahta R, Trent S, Yang C, and Schmidt EV. Epidermal Growth Factor Receptor expression is a candidate target of the synergistic combination of trastuzumab and flavopiridol in breast cancer. Cancer Res 63: 3626-3631, 2003.

4. Esteva FJ, Sahin AA, Rassidakis GZ, Yuan L, Smith TL, Yang Y, Gilcrease M, Cristofanilli M, Nahta R, Pusztai L, and Claret FX. Jun activating domain-binding protein 1 (JAB1) expression is associated with low $p27^{kip1}$ in node-negative breast cancer. Clinical Cancer Res 9: 5652-5659, 2003.

5. Nahta R and Esteva FJ. In vitro effects of trastuzumab and vinorelbine in trastuzumab- resistant breast cancer cells. Cancer Chemother. Pharmacol 53: 186-190, 2004.

6. Esteva FJ, Sahin AA, Smith TL, Yang Y, Pusztai L, Nahta R, Buzdar AU, Hortobagyi GN, and Bacus SS. Prognostic significance of phosphorylated P38 MAPK and HER-2 expression in node-positive breast cancer. Cancer 100: 499-506, 2004.

7. Nahta R, Hung MC, and Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. Cancer Res 64: 2343-2346, 2004.

8. Nahta R, Takahashi T, Ueno NT, Hung MC, and Esteva FJ. P27kip1 downregulation is associated with trastuzumab resistance in breast cancer cells. Cancer Res 64: 3981-3986, 2004.

9. Wang W, Nahta R, Huprun G, and Marks JR. $TAF_{II}70$ isoform specific growth suppression correlates with its ability to complex with the GADD45 protein. Mol Cancer Res 2: 442-452, 2004.
(The first two authors contributed equally to this work.)

10. #Nahta R, Yuan LXH, Zhang B, Kobayashi R, and #Esteva FJ. Insulin-like Growth Factor-I Receptor/Human Epidermal Growth Factor Receptor 2 Heterodimerization Contributes to Trastuzumab Resistance of Breast Cancer Cells. Cancer Res 65: 11118-11128, 2005. (#corresponding authors)

11. #Nahta R, Yuan LXH, Fiterman DJ, Zhang L, Ueno NT, Symmans WF, and #Esteva FJ. B-Cell Translocation Gene 1 (BTG1) Contributes to Antisense Bcl-2-Mediated Apoptosis in Breast Cancer Cells, Mol Cancer Ther 5: 1593-1601, 2006. (#corresponding authors)

12. Itamochi H, Kigawa J, Kanamori Y, Oishi T, Bartholomeusz C, Nahta R, Esteva FJ, Sneige N, Terakawa N, Ueno NT. Adenovirus Type 5 E1A Gene Therapy for Ovarian Clear Cell Carcinoma: A Potential Treatment Strategy. Mol Cancer Ther 6: 227-235, 2007.

13. #Nahta R, Yuan LXH, Du Y, and #Esteva FJ. Lapatinib induces apoptosis in trastuzumab-resistant breast cancer cells: effects on IGF-I signaling. Mol Cancer Ther 6: 667-674, 2007. (#corresponding authors)

Invited review articles

1. Nahta R, Hortobagyi GN, and Esteva FJ. Growth factor receptors in breast cancer: potential for therapeutic intervention. The Oncologist 8: 5-17, 2003.

2. Nahta R, Hortobagyi GN, and Esteva FJ. Signal transduction inhibitors in the treatment of breast cancer. Curr. Med. Chem. Anti-Cancer Agents 3: 201-216, 2003.

3. Nahta R, Hortobagyi GN, and Esteva FJ. Novel pharmacological approaches in the treatment of breast cancer. Expert Opin. Investig. Drugs 12: 909-921, 2003.

4. Nahta R and Esteva FJ. Bcl-2 antisense-based therapy for breast cancer. Semin. Oncol. 30 (Suppl 16): 143-149, 2003.

5. Nahta R and Esteva FJ. HER-2-targeted therapy: lessons learned and future directions. Clin. Cancer Res. 9: 5078-5084, 2003.

6. Nahta R and Esteva FJ. Herceptin: Mechanisms of action and resistance. Cancer Letters 232: 123-138, 2006 [E-pub 30 Mar 2005]

7. #Nahta R, Yu D, Hung MC, Hortobagyi GN, and #Esteva FJ. Mechanisms of Disease: understanding resistance to HER2-targeted therapy in human breast cancer. Nature Clinical Practice Oncology 3: 269-280, 2006. (#corresponding authors)

8. #Nahta R and #Esteva FJ. Molecular mechanisms of trastuzumab resistance. Breast Cancer Research 8: 215, E-pub 6 Nov 2006. (#corresponding authors)

9. #Nahta R and #Esteva FJ. Trastuzumab: Triumphs and Tribulations. Oncogene, 2007, in press. (#corresponding authors)

C. Research Support

Ongoing Research Support

K01 CA118174 Nahta (PI) 8/01/2006-7/31/2011
NIH/NCI
HER-2/IGF-IR cross-talk and Herceptin resistance
This study investigates interaction and cross talk between HER-2 and IGF-IR as a potential molecular mechanism of Herceptin resistance.
Role: PI

W81XWH 0610452 (BC050796) Nahta (PI) 3/20/2006-3/19/2009
U. S. Department of Defense (DOD)
IDEA Award
Crosstalk between leptin receptor and IGF-IR in breast cancer: a potential mediator of chemoresistance

This study investigates potential interaction and cross talk between the IGF-I receptor and the leptin receptor and how this contributes to resistance to taxane chemotherapy.
Role: PI

Pending

None